

REMARKS

This Amendment and Remarks are filed in response to the Final Office Action Dated February 23. The response is filed withing two months shortened statutory period in an attempt to overcome the Examiner's final rejections and to submit claims in suitable conditions for allowance.

Status of the Claims

Claims 1-62 are canceled.

The new claims 63-78 take in considerations Examiner's rejections. No new matter is added.

Rejections under 35 U.S.C. 112, Second Paragraph

Claims 43-62 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The Examiner argues that the claims are confusing in that they do not set forth clear process steps.

Applicants have rectified this problem by canceling claims 43-62 and replacing these claims with new claim 63-78.

The independent claim 63 is directed to an implantable construct prepared by a process where the process steps needed to derive the construct of the invention are clearly identified as suggested by the Examiner.

Claims 64-78, that have been newly added and are dependent on Claim 63, also take in consideration Examiner's suggestions and rejections. These claims track prior claims 44-62, but are product by process claims.

In the office action, the Examiner has listed a number of concerns with respect to Claim 43. Specifically, he states it is unclear after which step the immature hyaline cartilage construct is obtained. As stated above, Applicants have canceled Claim 43 and replaced it with new Claim 63.

In Claim 63, it is clear that the construct is formed at the completion of the activation step (e), where, at that stage, the previously inactive and non-dividing mature chondrocytes that are unable to synthesize a new extracellular matrix needed for repair of the injured cartilage, are activated and rejuvenated to a point when they begin to function as immature chondrocytes and regain their ability to synthesize a new extracellular matrix. These rejuvenated chondrocytes are thus reverted into their immature state when they have had such an ability.

The rejuvenation of the mature chondrocytes has not been disclosed or recognized in any of the cited art and is not implied from the cited references. None of the references recognized that the inactive chondrocytes may be converted into the active chondrocytes by submitting these inactive chondrocytes to a process according to the invention within the defined support matrix and under the defined process conditions.

The specification discloses an implantable construct comprising these rejuvenated chondrocytes and, because such construct functionally resembles behavior of the immature

cartilage, calls this construct neo-cartilage. Following the activation process (see claim 63) and upon implantation of the resulting construct, this neo-cartilage construct is able to produce and to continue to produce the extracellular matrix thereby forming the new cartilage that is or resembles the healthy hyaline cartilage. Such construct has been shown, upon implantation, to be incorporated into the healthy surrounding cartilage.

The invention thus provides the construct that is suitable for implantation, by recognizing the possibility of rejuvenating inactive chondrocytes and developing a process and conditions for activation of these inactive chondrocytes within constraints of the support matrix. The process and conditions are described in section describing "neo-cartilage", that is the rejuvenated cartilage, specifically on pages 20-22.

Since Examiner objects to use of the terms "neo-cartilage" and "immature" as uncertain as to their meaning and scope and not being definite, such terms have been canceled from the claims. Applicants submit, however, that these terms clearly distinguish the construct of this invention from the cited prior art that does not deal with, recognize, suggests or implies a construct comprising the rejuvenated chondrocytes.

Examiner also rejects Claim 43 as being unclear after which step the immature hyaline cartilage construct is obtained. This question has been answered above. However, Examiner further argues

that if the immature hyaline cartilage has the ratio in the last line of claim 43, this should be made clear and, furthermore, Examiner argues, if the ratio of immature hyaline cartilage is lower than 95:5 (last line of claim 43) and the ratio of mature hyaline cartilage is 95:5, immature hyaline cartilage having a ratio only slightly lower than 95:5 will be essentially the same as mature hyaline cartilage, and indistinguishable therefrom.

Applicants disagree. The construct of the invention as identified in the claim 63, is originally composed solely of the support matrix and chondrocytes. In the matrix seeded with chondrocytes, there is no extracellular matrix. Following the activation step, the extracellular matrix begins to be synthesized by rejuvenated chondrocytes. Consequently, at the beginning of the activation process, there is no extracellular matrix so the ratio of chondrocytes to the extracellular matrix is 100:0. During the activation process, the extracellular matrix is being synthesized and therefore the ratio of the chondrocytes to the extracellular matrix is decreasing. The aim of the invention is to for rejuvenated chondrocytes to synthesize enough extracellular matrix to end up with a normal healthy hyaline cartilage when such construct is first activated and then implanted into the cartilage lesion where the rejuvenated chondrocytes continue to synthesize the extracellular matrix until the construct is fully integrated into the surrounding healthy cartilage. Such integration has been

described to occur and is shown in, for example, Figure 12A, 12B, and 12C, among others.

Consequently, in the claim 63, the construct is described as comprising more than 5% of activated chondrocytes and the ratio of the extracellular matrix to chondrocytes as lower than 95:5. Percentage term "%", previously appearing in the claim 43 for the ratio has been canceled as being inappropriately used as indicated by the Examiner.

In the Office Action the Examiner states that Claim 43 is unclear in that it provides for a constant hydrostatic pressure having a certain frequency and asks: "How can a constant pressure have a frequency" and suggests that there does seem to be an inconsistency there.

Applicants disagree, however, to advance the prosecution, they canceled Claim 43 and added new Claim 63. The new Claim 63 does not claim the constant hydrostatic pressures.

However, Examiner clearly misunderstands the terms "constant" and "cyclic" hydrostatic pressure. Both cyclic and constant pressures are pressures of between 0.01-10 MPa above the hydrostatic pressure. Both these pressures, when applied, are applied at certain frequency, as defined in the claims. Each of these pressures has a certain frequency at which it is applied. The only difference is that one is applied as a constant, that is unchanging non-sigmoidal curve pressure, at certain frequency and

the other is applied in cycles, that is in a sigmoidal curve that models the S-curve, also at certain frequency. Such frequency is defined as a very short but measurable interval when the pressure is applied. Since the term has been deleted, this point is now moot, however, Examiner will note that the constant hydrostatic pressure also has an effect on the chondrocytes activation, albeit not as high as the cyclic pressure (see, for example, Table 5, page 57).

This Table also supports Applicants argument that the chondrocytes are activated and rejuvenated. Production of S-GAG and content of DNA in the construct clearly shows that the currently described activation results in production of the new extracellular matrix. Already at 7 day of the process, the production of S-GAG is significantly higher than the level of S-GAG at day zero and also vis-avis control and is even more pronounced at day 21.

Examiner also argues that in the last line of claim 43, reciting "the neo-cartilage construct" does not have clear antecedent basis since line 1 of the claim requires an immature hyaline cartilage construct.

Applicants disagree, however, the new claims do not utilize this term.

Claim 48 is deemed to be unclear as to when in claim 43 the chondrocytes are in a gel as required. How does the gel relate to

the support matrix in claim 43? Is the gel the matrix?

Applicants disagree, however, the term is either deleted or is clarified in the new claims.

Claim 49 is unclear how a collagen gel can be a collagen solution.

Applicants disagree, the collagen gel can be in the solution, however, the new claims are corrected to separate the two.

In line 2 of claim 51, "sol-gel" is not a material that can be a matrix. Sol-gel defines a process and not a material. It is suggested the claim recite "gelled sol".

Applicants disagree. The new claims do not utilize this term.

Claim 52 is unclear how fibronectin, laminin, bioactive peptide, growth factor, cytokine form the matrix. These are not materials that normally form a matrix. In the last line of the claim, "a copolymer thereof" is unclear as to materials referred to as being a copolymer. Is copolymer thereof referring to all previous materials recited? Furthermore, all of the materials recited before "copolymer thereof" are not materials that normally form a copolymer, and how the materials form a copolymer is unclear.

Applicants disagree. Examiner is misunderstanding the claimed compositions. It is not fibronectin or laminin, etc, that is used alone for matrix formation. It is "a collagen **containing**" fibronectin, laminin, etc. The "copolymer" term is canceled.

In claims 57 and 58, there is not clear antecedent basis for "the metabolic activation".

Applicants disagree. The "metabolic" term does not appear in new claims.

In claims 59 and 60, there is not clear antecedent basis for "the support matrix construct".

Applicants disagree. Claims are canceled.

Claim 61 is unclear as to whether the medium is the perfusion medium of claim 43 or some other medium. It is suggested the claim be amended in line 2 by changing "a medium" to --- said perfusion medium and changing "a medium perfusion" to --- perfusion medium.

Applicants appreciate Examiner's suggestion, and to meet Examiner's rejections, Applicants utilize the suggested terms in the new claims.

In the last line of claim 61, "insulin-transferring-sodium selenite" is uncertain as to how insulin-transferring defines sodium selenite. Insulin is not required in the process of claim 61, and insulin transfer cannot occur. Furthermore, sodium selenite is the same compound irrespective of whether insulin transfer occurs, and "insulin-transferring" does not limit the composition of sodium selenite. It is suggested "insulin-transferring" be deleted.

Applicants disagree. However, the claim is canceled and the new claims do not claim this compound.

It is respectfully submitted that with the submission of the new claims, the Examiner's rejections under 35 U.S.C. 112, second paragraph have been addressed and that the newly submitted claims overcome these rejections.

It is believed that the new claims meet Examiner's rejections and that the rejections under 35 U.S.C 112, second paragraph are overcome and should be withdrawn. It is so respectfully requested.

Rejections under 35 U.S.C 102 and 103

Claims 43-47 and 44-62 have been rejected under 35 U.S.C. 102(a) as being anticipated by Smith et al. (6,528,052) or as being unpatentable over Smith (above) and Burg, Atkins, Bachrach and further in view of Bellamkonda.

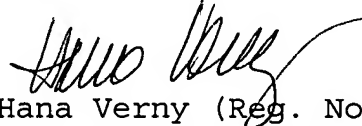
Applicants respectfully submit that with the cancellation of Claims 43-62 and with submission of the new claims, these rejections are no longer valid. The reason is that Applicants are now claiming a construct comprising rejuvenated chondrocytes made by the process of making such a construct. Neither Smith nor other cited references disclose or suggest the construct comprising rejuvenated chondrocytes able to produce a new extracellular matrix produced by the process claimed herein.

Applicants respectfully submit that not only is the process inventive, but also the product made by that process is inventive.

SUMMARY

In summary, Applicants canceled claims 1-62 and submit herewith the new claims 63-78. It is respectfully submitted that the new claims presently in the application are allowable. Notice of allowance is respectfully solicited.

Respectfully submitted,



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Date: April 23, 2007

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